Complete Summary

GUIDELINE TITLE

Optimal therapy for patients diagnosed with multiple myeloma and the role of high-dose chemotherapy and stem cell support.

BIBLIOGRAPHIC SOURCE(S)

Cancer Care Ontario Practice Guideline Initiative (CCOPGI). Optimal therapy for patients diagnosed with multiple myeloma and the role of high-dose chemotherapy and stem cell support [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2002 Apr [online update]. Various p. (Practice guideline; no. 6-6). [90 references]

Imrie K, Esmail R, Meyer RM. The role of high-dose chemotherapy and stem-cell transplantation in patients with multiple myeloma: a practice guideline of the Cancer Care Ontario Practice Guidelines Initiative. Ann Intern Med 2002 Apr 16;136(8):619-29. [44 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Multiple myeloma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Hematology
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To make recommendations regarding the use of high-dose chemotherapy and peripheral stem cell or bone marrow transplantation for patients with multiple myeloma

TARGET POPULATION

Adult patients with advanced-stage multiple myeloma and good performance status

INTERVENTIONS AND PRACTICES CONSIDERED

1. Conventional chemotherapy with oral melphalan and prednisone
2. Multi-agent intravenous chemotherapy including a combination of one or more alkylating agents, such as melphalan, BCNU (carmustine), or cyclophosphamide; e.g., VMCP/BVAP (vincristine, melphalan, cyclophosphamide, and prednisone/vincristine, carmustine, doxorubicin, and prednisone)
3. High-dose glucocorticoid-based chemotherapy, such as vincristine, doxorubicin (Adriamycin), and dexamethasone (VAD), without alkylating agents
4. Interferon alpha

   Note: The guideline developers were unable to reach consensus about the use of interferon.

5. Total body irradiation (TBI)

   Note: For patients undergoing autologous stem cell transplantation as part of standard therapy, it is recommended that the transplantation regimen include melphalan without total body irradiation.

6. Allogeneic bone marrow transplantation (alloBMT)

   Note: Allogeneic transplantation is not recommended outside of a clinical trial.

7. Autologous bone marrow transplantation (ABMT)
8. Peripheral blood stem cell transplantation (PBST)
9. Early versus late transplantation
10. Single versus double (i.e., tandem) transplantation

MAJOR OUTCOMES CONSIDERED

- Response rates to treatment
- Survival (overall, median, event-free, or progression-free)
- Treatment-related toxicity and mortality
- Incremental effectiveness (ratio of incremental cost and incremental effectiveness)
- Marginal cost-effectiveness ratio
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

2000 Guideline

MEDLINE, CANCERLIT and the Cochrane Library databases were searched from 1992 to December 1997. This search was updated in October 1998, June 1999, and April 2000. "Multiple myeloma" (MeSH and text word) was combined with "bone marrow transplantation" (MeSH and text word) and drug therapy (MeSH). These terms were then combined with the search terms for the following study designs: practice guidelines, systematic reviews or meta-analyses, reviews, randomized controlled trials, controlled clinical trials and comparative studies. In addition, Pubmed, the Physician Data Query (PDQ) database (www.cancer.gov/search/clinical_trials), relevant conference proceedings (American Society of Hematology, 1997, 1998, 1999 and American Society of Clinical Oncology, 1999), article bibliographies and personal files were reviewed. To address the issue of optimal chemotherapy, an additional search was performed of the same databases using "multiple myeloma" (MeSH) combined with "randomized controlled trials" (MeSH) and the text word "random:" in the title.

2002 Update

The original literature search has been updated using MEDLINE (through January 2002), CANCERLIT (through October 2001), the Cochrane Library (2002, Issue 1), the proceedings of the annual meetings of the American Society of Clinical Oncology (2000 and 2001) and the American Society of Hematology (2001), and the abstracts of the VIIIth International Myeloma Workshop. The PDQ database was also searched to determine the status of the ongoing trials reported in the original practice guideline report, and to search for any new ongoing trials.

Inclusion Criteria

Articles were selected based on the following criteria:

1. Randomized controlled trials (RCTs) of patients with multiple myeloma that reported on the outcomes of survival and/or quality of life.
2. Non-randomized trials were included if they had appropriate contemporaneous control groups and reported on the outcomes of survival and/or quality of life.
3. Study results were used to estimate both the potential efficacy and appropriate timing of autologous and allogeneic transplantation. Meta-analyses, systematic reviews and economic analyses were also included. Because of insufficient data addressing the specifics of the transplant manoeuvre and which patients would be most likely to benefit from transplantation, a second literature search was performed to include data from single-arm studies.

NUMBER OF SOURCE DOCUMENTS

2000 Guideline

69 papers met the criteria for inclusion.

2002 Update

10 reports were identified in the update process.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

2000 Guideline

As the nine randomized controlled trials on transplantation addressed different questions, statistical pooling of data was not attempted.

2002 Update

The Disease Site Group (DSG) recognized that the pooling of data comparing standard-dose therapy with high dose therapy and autologous transplantation

may be feasible. The Disease Site Group will review whether conducting a published data meta-analysis is appropriate when the results of recently reported abstract publications are reported in article form.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

December 2000 Guideline

The Hematology Disease Site Group (DSG) was asked to develop a broad guideline on the management of patients with multiple myeloma. The DSG considered the potential of developing a more comprehensive guideline and concluded that the complexity and importance of the high-dose therapy transplant topic warranted a specific guideline; the possibility remains for subsequently merging this guideline into a document dealing with a wider range of issues in myeloma.

On appraising the published literature regarding transplant therapy, there were two major issues that yielded considerable debate. The first issue related to the quality and volume of data assessing the transplant question. Specifically, debate centered on the strength of the recommendation for transplantation given that the supporting data were limited to only one well-conducted positive randomized trial. After careful consideration, there was unanimous agreement that patients ought to be informed about the results of this study and this was reflected in the wording of the recommendations. There was further discussion about whether there was sufficient evidence to not only offer, but to "recommend" this treatment as the preferred therapeutic option. While the DSG felt that patients should have a choice, they felt that that the current evidence is sufficient to warrant the "recommend" terminology.

The second point of debate dealt with the role of interferon. Some members of the group felt that as interferon was part of the treatment maneuver in the Attal study, and was reported by Cunningham et al to result in superior time-to-disease progression, the use of interferon should be included in transplant treatment strategies. Other members felt that in the absence of data demonstrating a survival advantage, the toxicity of this agent precludes routine use. The DSG was unable to reach consensus and a recommendation about using interferon was therefore not included.

The DSG members considered whether a firm recommendation should be made regarding the timing of transplantation. Members felt that the best available evidence found a survival benefit when transplantation was used as part of the initial therapy. In a randomized trial of early versus delayed transplantation in patients in whom stem cells had been collected at diagnosis, delaying transplant did not shorten survival although there was a suggestion that quality of life was adversely affected; however the 95% confidence intervals overlapped. For this reason, the DSG members did not feel that a strong recommendation could be made regarding the timing of transplantation, although there was consensus that

if a delayed transplant is contemplated, stem cells should be collected soon after diagnosis.

The initial draft recommendations were circulated for practitioner feedback in May 1999 and received wide support. The initial Practice Guideline was approved by the Practice Guidelines Coordinating Committee in October 1999. Since the release of the initial guideline, new data emerged in abstract form that included assessment of the role of total-body irradiation (TBI) and a further randomized trial evaluating autologous transplantation in patients over age 55 years.

The DSG concluded that the study comparing melphalan 140 mg/m^2 plus total-body irradiation with melphalan 200 mg/m^2 required modification of the previous recommendation regarding the details of the high-dose therapy regimen (bullet five). The reworded recommendation now permits either option (see "Major Recommendations" field). There was considerable discussion regarding the results of the report by Fermand et al. This trial, published in abstract form, compared a transplant strategy with standard dose treatment in patients 55 years and greater and failed to detect a survival benefit. The DSG considered whether these data should lead to a rewording of the overall recommendation regarding "offering" versus "recommending" high-dose therapy transplantation and/or whether an age restriction should be suggested. The DSG concluded that while the Fermand trial was large and appeared to be well conducted, insufficient information was provided in the abstract to change the initial recommendations. However, the wording of the new recommendation (bullet one) highlights the indication by age. The DSG acknowledges that the final results of the Fermand trial and other ongoing studies may influence the nature and wording of the recommendations in the future.

The DSG did not consider these new data and the resulting modifications sufficiently different from the initial guideline to warrant another cycle of practitioner feedback. This revised guideline was circulated to the Practice Guidelines Coordinating Committee.

April 2002 Update

The Hematology DSG's evaluation of new evidence resulted in extensive discussions of two topics: the role of autologous stem cell transplantation in comparison with standard-dose therapy and the nature of the high-dose therapy regimen.

The DSG concluded that the evidence demonstrating that autologous transplantation results in superior survival in comparison with standard–dose therapy is now weaker: the preliminary results of the randomized trial conducted by the Spanish Cooperative Group (PETHEMA) trial failed to demonstrate a difference in disease control or overall survival. However, this trial is reported in preliminary abstract form and with a limited median follow-up of 42 months. Similar preliminary results were previously reported by Fermand, which did not contribute to the original practice guideline recommendation. The DSG concluded, therefore, that while potentially important, these results are not sufficient to warrant a change in the previous recommendation. There was again debate regarding whether transplantation should be "recommended" or "offered" to appropriate patients; consensus was reached to maintain the wording of the original version of the guideline to recommend transplantation, and that this

recommendation is strongest for patients less than 55 years of age who have normal renal function. The DSG recognizes that future evaluations will include reports of mature results of the new evidence described in this update, results of active trials, and systematic reviews that include a meta-analysis of available data.

Given the updated evidence regarding high-dose therapy preparative regimens, the DSG unanimously concluded that melphalan 200 mg/m^2 as a single modality should be the recommended regimen for patients undergoing autologous transplantation outside of a clinical trial setting. In comparison with melphalan 140 mg/m^2 and total body radiation, melphalan given as 200 mg/m^2 was associated with superior survival, less toxicity, and was less resource intensive.

The DSG concluded that the new data assessing the roles of double (tandem) transplantation and post–transplantation therapy with interferon–alpha were insufficient to change previous conclusions and recommendations.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A cost-effectiveness analysis using survival data reported in five large published randomized controlled trials on induction treatment evaluated the incremental cost-effectiveness ratio [the ratio of incremental cost and incremental effectiveness (where incremental cost is the lifetime cost difference between treated patients and controls, and incremental effectiveness is the lifetime survival difference between the two patient groups)]. The mean lifetime duration of survival was 3.47 years for melphalan at conventional doses without interferon, 3.74 years for melphalan at conventional doses with interferon and 7.28 years for autologous bone marrow transplantation (ABMT). Survival was significantly better for patients undergoing ABMT versus melphalan treatment (relative risk reduction=54%, 95% confidence interval [CI], 46% to 59%; $p<0.05$). Survival after combined melphalan and interferon treatment was not significantly different from melphalan alone ($p>0.05$). The marginal cost-effectiveness ratio of autologous transplantation was approximately an additional $26 000 per life year gained compared with conventional treatment with melphalan.

Economic analyses based on trials that collect data on cost as part of their primary data collection are less susceptible to methodological errors. This economic analysis collected and pooled data from information available in the published literature. Based on the critical appraisal done by the Guidelines Initiative, wethe guideline developers have determined it to be methodologically rigorous. Therefore, the impact of ABMT compared with conventional treatment with melphalan can be considered to be favourable in terms of cost-effectiveness ratio.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 221 practitioners (94 hematologists, 93 medical oncologists, and 24 radiation oncologists) in Ontario, with a 71% return rate. The survey consisted of items asking for ratings on the quality of the draft practice guideline, and whether the draft recommendations should be approved as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary. The recommendations that follow are based on the previous version of the guideline.

- Autologous transplantation is recommended for patients with advanced-stage myeloma and good performance status. The evidence is strongest for patients under 55 years of age without significant renal dysfunction following hydration and remission-induction chemotherapy. Physicians must use their clinical judgement in recommending transplantation to patients over 55 years of age or those with renal impairment.
- There is insufficient evidence to recommend allogeneic transplantation as routine therapy for multiple myeloma.
- Patients who are potentially eligible for transplantation should be referred for transplant assessment early after diagnosis and should not be given extensive exposure to alkylating agents such as melphalan prior to the collection of stem cells. High-dose glucocorticoid based regimens such as vincristine, doxorubicin (Adriamycin), dexamethasone (VAD) are preferable for such patients.
- Harvesting of autologous peripheral blood stem cells or bone marrow should be performed early in the patient´s treatment course. The best available data demonstrate that transplantation is most advantageous when performed as part of the initial therapy.
- No conclusions can be reached about the role of interferon alpha following transplantation at this time.
- For patients undergoing autologous stem cell transplantation as part of standard therapy, it is recommended that the transplantation regimen include melphalan 200 mg/m^2 without total body radiation.
- There is insufficient evidence to recommend a treatment plan that includes two transplants performed in succession (tandem transplantation) outside of a clinical trial.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Evidence included in the original practice guideline report according to study questions

What is optimal conventional chemotherapy?

4 meta-analyses, 30 randomized controlled trials (RCTs)

Transplantation versus chemotherapy

2 RCTs, 3 non-randomized comparisons (NRCs), 1 economic analysis

Relative efficacy of autologous & allogeneic transplantation

3 NRCs

Specifics of the manoeuvre

6 RCTs, 4 NRCs, 2 single-arm studies (SAS), 2 economic analyses

When should it be done?

1 RCT, 2 NRCs

Who should be transplanted?

2 RCTs, 7 NRCs, 2 SAS

2002 Update

What is optimal conventional chemotherapy?

Not evaluated

Transplantation versus chemotherapy

2 randomized trials (abstracts)

Relative efficacy of autologous & allogeneic transplantation

1 non-randomized comparison (article) - a retrospective cohort comparison

Specifics of the manoeuvre

6 randomized trials (3 articles and 3 abstracts); 1 non-randomized comparison (article)

When should it be done?

No reports identified

Who should be transplanted?

No reports identified

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- One randomized controlled trial (RCT) found autologous bone marrow transplantation (ABMT) prolonged survival in newly diagnosed patients under the age of 65 with advanced stage disease compared with conventional chemotherapy with interferon alpha (five-year survival, 52% versus 12%; p=0.03).
- A randomized controlled trial in abstract form comparing bone marrow to peripheral bloods stem cell infusion found that patients undergoing peripheral blood stem cell transplantation had faster engraftment (9.7 days versus 12.2 days; p<0.001). However, toxic death rates, response rates, and two-year survival were not significantly different.
- Three non-randomized comparisons of autologous and allogeneic transplantation found autologous transplantation to be less toxic and associated with at least equivalent survival.
- In an updated report of the randomized trial comparing combination therapy with melphalan 140 mg/m^2 and total body irradiation (TBI) with melphalan 200 mg/mg^2 as a single modality, survival at 45 months was superior in the group assigned to receive melphalan 200 mg/mg^2 (65.8% versus 55%; p=0.05). In addition, patients assigned to receive melphalan 200 mg/mg^2 experienced less severe mucositis, required fewer transfusions, and had shorter durations of hospitalization and intravenous antibiotic administration.

Subgroups Most Likely to Benefit:

For autologous transplantation in advanced-stage multiple myeloma patients with good performance status, evidence of benefit is strongest for patients who are younger than 55 years of age and have a serum creatinine level less than 150 micromoles/L.

POTENTIAL HARMS

- Treatment-related mortality is a significant problem with allogeneic transplantation. Three non-randomized comparisons of autologous and allogeneic transplantation found autologous transplantation to be less toxic and associated with at least equivalent survival.
- The effect of prior alkylating agent exposure on bone marrow harvesting is not clear. However, alkylating agent exposure adversely affects peripheral blood stem cell yield and engraftment following autologous stem cell transplantation (ASCT). If stem cell transplantation is considered, patients should not be given extensive exposure to melphalan or other alkylating

agents prior to stem cell collection. High-dose glucocorticoid-based regiments such as VAD (vincristine, doxorubicin [Adriamycin], dexamethasone) may be preferable for such patients.

- A randomized controlled trial (RCT) in abstract form that compared high-dose melphalan plus total body irradiation (TBI) versus high-dose melphalan did not find a difference in terms of response and two-year event-free survival, but toxicity was significantly greater for patients receiving the total body irradiation regimen.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Cancer Care Ontario Practice Guideline Initiative (CCOPGI). Optimal therapy for patients diagnosed with multiple myeloma and the role of high-dose chemotherapy and stem cell support [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2002 Apr [online update]. Various p. (Practice guideline; no. 6-6). [90 references]

Imrie K, Esmail R, Meyer RM. The role of high-dose chemotherapy and stem-cell transplantation in patients with multiple myeloma: a practice guideline of the Cancer Care Ontario Practice Guidelines Initiative. Ann Intern Med 2002 Apr 16;136(8):619-29. [44 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000 Dec 22 (revised online 2002 Apr)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario, Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Hematology Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Members of the Hematology Disease Site Group: Dr. R. Meyer, Chair, Hematologist; *Dr. H. Abu Zahra, Medical Oncologist; Dr. I. Chin-Yee, Hematologist; Ms. B. Costello, Community Representative; Dr. R. M. Crump, Medical Oncologist; *Dr. C. deMetz, Radiation Oncologist; *Dr. P. Galbraith, Hematologist; Dr. M. Gospodarowicz, Radiation Oncologist; Dr. L. Huebsch, Hematologist; Dr. K. Imrie, Hematologist; Mr. M. Kacsor, Community Representative; Dr. L. Kaizer, Medical Oncologist; Dr. T. Kouroukis, Hematologist; Dr. J. MacEachern, Hematology Fellow; Dr. J. Matthews, Hematologist, Queen´s University, Kingston; Dr. J. Meharchand, Hematologist; Dr. H. Messner, Medical Oncologist; Dr. N. Shehata, Hematology Fellow; Dr. A. Smith, Hematologist; Dr. J. Sussman, Radiation Oncologist; Dr. I. Walker, Hematologist; Dr. K. Yee, Hematology Resident

Resource group members working with the Hematology Disease Site Group: Faculty: *Dr. C. Sawka; Staff: *Ms. Rosmin Esmail, *Ms. Lubna Baig, *Ms. Julie Makarski, Ms. Adrienne Stevens

*Members that have completed their term with Hematology Disease Site Group

For a current list of members, please visit the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Hematology Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

Note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

GUIDELINE AVAILABILITY

Electronic copies of the updated guideline: Available from the Practice Guidelines Initiative Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Optimal therapy for patients diagnosed with multiple myeloma and the role of high-dose chemotherapy and stem cell support. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2000 Dec 22 (updated online 2002 Apr). Electronic copies: Available from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on October 29, 2002. The information was verified by the guideline developer on November 15, 2002.

COPYRIGHT STATEMENT

Date Modified: 5/3/2004